Sepsis in 2024: a review

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Abstract

Sepsis is responsible for tremendous morbidity, mortality, and healthcare expenditure worldwide. Over the past decade, the conceptualization of sepsis has shifted from one based upon an inflammatory response to one defined by a dysregulated immune response to infection and resulting organ dysfunction. The definitions of sepsis and septic shock were revised to improve their diagnostic specificity and facilitate accurate and timely diagnoses at the bedside. The core of sepsis management remains *early* identification and diagnostic testing, *early* antimicrobial therapy, and *early* haemodynamic resuscitation. Recently, there has been additional movement towards classifying and treating sepsis based on genotype, phenotype, and endotype, though these methods are not yet widely accessible or adopted. Current guidelines recommend that the first steps in treatment and resuscitation take place within *1 hour* from when septic shock is suspected. Additional essential elements in the current sepsis management guidelines include using dynamic parameters to assess fluid responsiveness, a conservative fluid strategy following initial resuscitation (with subsequent de-resuscitation when possible), serial reassessments of haemodynamic status, and adaptable treatment plans. This review provides a summary of the most recent clinical trials and practice guidelines for the diagnosis and treatment of sepsis in the critical care setting.

Keywords Critical care; intensive care; sepsis; septic shock

Royal College of Anaesthetists CPD Skills Framework: ICM and emergency management

Learning objectives

After reading this article, you should be able to:

- define sepsis and septic shock using the most contemporary (Sepsis-3) criteria
- describe clinical criteria required for the early diagnosis of sepsis
- formulate an initial treatment plan for the critically ill patient with sepsis
- describe secondary and adjunctive therapies presently available for refractory sepsis

Introduction

In 2017 alone, the global incidence of sepsis was estimated to be 48.9 million cases and was associated with 11 million deaths, thus representing 19.7% of all deaths worldwide.[1] More regionally, data from the NHS showed 244,158 cases of sepsis with 48,000 deaths in the UK during the same time period. The annual economic burden (both direct and indirect) is estimated at a staggering £7.42 billion.[2] More timely and accurate recognition of patients at risk for sepsis is essential to improving patient care and health system outcomes. To that end, this article will review the most recent definitions and clinical guidelines for the treatment of sepsis.

Pathophysiology of sepsis

At its onset, sepsis manifests as an overwhelming release of inflammatory mediators (sometimes referred to as 'cytokine storm') in response to an infection. An analogy can be drawn between the immune response to infection and national defences. Components of the innate immune system or 'citizens' (epithelial cells, macrophages, mast cells, innate lymphocytes) at the site of pathogen exposure activate and recruit circulating immune cells or 'troopers' (neutrophils, Natural Killer (NK) cells, dendritic cells, platelets, monocytes, eosinophils). These cells have pathogen-recognition receptors (PRRs) on their surface which bind to and are activated by pathogen-associated molecular patterns (PAMPs) on bacterial cell walls or damage-associated molecular patterns (DAMPs) – host biomolecules released when danger is sensed from a pathogen, burn, trauma, etc. This receptor binding initiates an intracellular signalling cascade resulting in the activation of cytosolic transcription factors such as nuclear factor-κB and activator protein 1 (AP-1), which in turn leads to the production of several acute phase reactants, among them cytokines, coagulation factors, and inducible nitric oxide synthetase, thus initiating the immunoinflammatory cascade. A subsequent chain reaction involves the activation of even stronger 'armed forces', the adaptive immune response. This explosive activation and resultant immune 'cytokine storm' are believed to be the causative pathway for septic shock.[3]

The end-response to an infection is often a combination of pro- and anti-inflammatory cascades. Once infection resolves, a balance is established between immune up-regulating and down-regulating processes, and immune memory is generated to protect against future exposures. However, when the initial response is excessive or dysregulated, this balancing process becomes dysfunctional. As sepsis persists, by about 24–48 hours a shift towards a hypoinflammatory state is observed, and patients develop features consistent with immunosuppression.

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This phase is known as sepsis-induced immunoparalysis,[4] and the majority of septic shock-related deaths occur during this immunoparalytic phase. These patients are often not able to clear the initial infection and, in addition, are predisposed to new infections from nosocomial pathogens. T-cell and B-cell exhaustion, apoptosis, and anergy are now recognized immunosuppressive mechanisms observed in patients with fatal sepsis.[5,6] Although the pattern of hyperinflammation/hyperimmunity followed by hypoinflammation/hypoimmunity is the most common presentation of sepsis, it should be noted that some patients present as hypoinflammatory/hypoimmune from the outset.[7]

Definitions

Over the course of the last few decades, considerable effort has been expended in improving the recognition, categorization, and algorithmic treatment of sepsis. From the early 1990s until the mid-2010s, sepsis was defined as a proven or suspected infection accompanied by a pronounced systemic inflammatory response syndrome (SIRS). Patients were further categorized as having sepsis, severe sepsis, or septic shock based on organ dysfunction and fluid responsiveness. Though widely accepted at the time, it failed to detect many cases of sepsis (as many as 1 in 8) and a more precise definition was required.[8]

The Third International Consensus Definitions for Sepsis and Septic Shock ('Sepsis-3'), jointly developed by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM), were released in 2016 and noted that sepsis is far more complex than an inflammatory response, involving both pro- *and* anti-inflammatory processes and non-immunologic systems in the disease process.[4] The term 'severe sepsis' was eliminated, and sepsis was formally redefined as 'life-threatening organ dysfunction caused by a dysregulated host response to infection'. Septic shock was redefined as a 'subset of sepsis in which profound circulatory failure, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone'.

In addition to the new definitions, the consensus committee also established a set of practical clinical guides to facilitate the diagnosis of sepsis at the bedside. Although earlier versions of these guidelines recommended the Sequential Organ Failure Analysis (SOFA) score or a 'qSOFA' variant (Box 1),[4] more recent studies have shown that these tools are sensitive but not specific for patients at risk for increased mortality from sepsis[9] and more recent guidelines have recommended against using these as single screening tools.[10]

Quick Sequential Organ Failure Analysis (qSOFA) score[a]

qSOFA criteria: ≥ 2 of the following:

- Respiratory rate >22/minute
- Change in mental status
- Systolic blood pressure <100 mmHg

[a] Adapted from: Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801–810.

Box 1

Management

The cornerstone of effective sepsis management is indisputably the timely identification of sepsis and the prompt initiation of aggressive and appropriate treatment. Successful treatment requires fluid resuscitation with a focus on perfusion and the early administration of antibiotics. The 2018 Surviving Sepsis Campaign (SSC) bundle update introduced the '1-Hour Bundle', which was largely retained for patients with *septic shock* in the 2021 SSC guidelines.[10] This bundle combines elements of the prior 3- and 6-Hour Bundles into an algorithm that emphasizes the *immediate* treatment of septic shock patients. The first elements of the bundle are diagnostic: measuring a lactate level and obtaining blood cultures *prior* to administration of antibiotics. The remainder of the bundle addresses management: early antimicrobial administration, fluid resuscitation, and, if required, vasopressor support (see Box 2).

The '1-Hour Bundle' was met with some resistance, however, and, despite observational data suggesting the importance of timely treatment of septic shock, there is a lack of high-quality prospective evidence supporting the shift.[11] Additionally, in the era of quality metrics, many groups have expressed concerns that compression of the timeline could lead to the overdiagnosis of sepsis and thus an overuse of antibiotics and excessive volume resuscitation.[12] The Effect of the 1-hour Sepsis Bundle on In-hospital Mortality in Patients With Sepsis in the Emergency Department: a Randomized Controlled Trial (1BED) is an ongoing multicentre randomized controlled trial (RCT) that aims to address this concern specifically.[13]

Early antimicrobial therapy and source control

For patients with presumed sepsis, early empiric broad-spectrum antibiotic therapy should be initiated within 1 hour of presentation, especially in patients with septic shock. Ideally, microbiological samples from all suspected foci of infection should be obtained prior to administering antibiotics. However, if obtaining these samples would delay antibiotic administration, antibiotic therapy should always take priority. Though this finding has not been reproduced in all studies, especially those analysing patients with sepsis without shock, the prompt administration of antibiotics has been independently associated with improved sepsis survival in multiple studies.[14,15] Appropriate empiric

Surviving Sepsis Campaign-1 Hour Bundle[a]

- Measure lactate level (follow serial measurements if initial level >2mmol/litre)
- Obtain blood cultures prior to administering antibiotics
- Administer broad spectrum antibiotics
- Begin rapid administration of 30 ml/kg of crystalloid for hypotension or lactate ≥4mmol/litre
- Start vasopressors if patient is hypotensive during or after fluid resuscitation to maintain a mean arterial pressure (MAP) 65≥mmHg

[a] Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Intensive care medicine. 2018 Jun 1;44(6):925–8.

Box 2

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antimicrobial therapy is essential for decreasing sepsis mortality and should be guided by the clinical presentation and local antimicrobial resistance patterns, as well as the patient's risk factors for particular organisms (see Table 1).[15,16] Chronic comorbidities (e.g. human immunodeficiency virus, combined variable immunodeficiency, diabetes mellitus) and the presence of invasive medical devices (e.g. central venous catheters, urinary catheters) should also be taken into account when selecting initial antibiotic regimens.

When the source of infection is unclear, empiric broad-spectrum antimicrobial therapy should be administered. For most patients, empiric antibiotic coverage should include either an extended spectrum penicillin, a third- or fourth-generation cephalosporin, or a carbapenem. Additional consideration should be paid to risk factors for meticillin-resistant *Staphylococcus aureus* (MRSA) and, if present, empiric vancomycin administration is advised. Combination therapy (the use of multiple antibiotics with different pharmacodynamic profiles and mechanisms of action to treat the same organism) is a topic of some debate, though some early studies reported a synergistic effect with the addition of an aminoglycoside to a β-lactam,[17] and later studies assessed the addition of a fluoroquinolone. Combination therapy has been associated with improved survival in the most critically ill patients,[18] though RCT data are lacking. In the appropriate clinical context (e.g. suspected influenza), empiric anti-viral therapy is appropriate. In the setting of immunosuppression, total parenteral nutrition, or recent abdominal surgery, empiric anti-fungal therapy can also be considered. Once microbial data are available, prompt de-escalation to a targeted antimicrobial is safe and is associated with lower mortality rates.[19]

Source control has been increasingly recognized as an important element of optimal sepsis treatment. The removal of potentially infected invasive devices is highly recommended, particularly urinary and central venous catheters. Prompt consultation with surgical or interventional radiology services is required to address scenarios such as an empyema, septic arthritis, cholecystitis, or intra-abdominal abscess. Generally, the least invasive intervention method of source control is preferred, though timeliness is also a major factor in selecting between competing options. A multidisciplinary approach to early intervention (<6 hours) is associated with improved patient survival.[20]

Fluid resuscitation

Prompt fluid resuscitation should be initiated upon the diagnosis of sepsis. Previous guidelines strongly recommend initiating the infusion of 30 ml/kg of intravenous (IV) crystalloid fluid within *1 hour* of sepsis identification if hypotension is present. However, recent updates have downgraded the strength of this recommended fluid volume.[10]

Fluid choice – colloid versus crystalloid: in 2004, the SAFE trial compared clinical outcomes in critically ill patients receiving volume resuscitation with either normal saline or albumin.[21] No significant difference in all-cause mortality was noted between the two groups, though a subgroup analysis showed increased mortality with albumin in patients with traumatic brain injury. The combination of the significantly increased expense of albumin infusion and an absence of data to support a clear benefit led the SSC to recommend crystalloids as the initial volume resuscitation agents of choice.

Comparison of Sepsis-2 and Sepsis-3[a]

	Sepsis-2	Sepsis-3
Publication year	2001	2016
Mechanism (pathophysiology)	**Physiological** inflammatory response (SIRS) to infection	**Dysregulated** immune response to infection
Spectrum	SIRS → Sepsis → Severe Sepsis → Septic shock → MODS	Sepsis → Septic shock
Predictive validity for in-hospital mortality (area under the curve, p <0.001)	0.64 (95% CI, 0.62–0.66)	0.74 (95% CI, 0.73–0.76)
Sensitivity/specificity	↑ Sensitivity ↓ Specificity	↓ Sensitivity ↑ Specificity
Definition of septic shock	Acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes	Subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality
Practical considerations	3 of 4 SIRS criteria obtainable at bedside without need for laboratory testing	Multiple laboratory test results required to calculate SOFA score; qSOFA can be used as substitute prior to test availability

MODS, multiple organ dysfunction syndrome; qSOFA, quick sequential organ failure analysis; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure analysis.

[a] Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801–810.

Table 1

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Fluid choice – saline versus balanced crystalloid: which crystalloid to use is also a matter of active debate. Two large single-centre cluster RCTs, including SMART which focused specifically on critically ill patients, found decreases in the composite outcome of mortality, renal dysfunction, and need for renal replacement therapy (RRT) with the use of balanced salt solutions such as Ringer's lactate or Plasma-Lyte when compared to 0.9% saline solution.[22,23] However, the more recent BaSICS and PLUS trials demonstrated no significant differences in 90-day mortality between the two arms, though a meta-analysis of 13 RCTs and more than 35,000 intensive care unit (ICU) patients (the majority of which came from the SMART, BaSICS, and PLUS trials) showed a small mortality benefit in favour of balanced solutions.[24–26]

Fluid balance: while adequate resuscitation is essential, fluid overload is associated with increased mortality,[27] making perfusion assessment essential to the treatment algorithm. Careful attention to fluid management with a transition to conservative fluid management 24–48 hours after successful resuscitation is associated with reduced ICU lengths of stay and increased ventilator-free days. Additionally, Silversides et al. found that a positive fluid balance at day 3 was an independent risk factor for increased mortality.[28] The CLASSIC and CLOVERS RCTs suggested that more conservative approaches to fluid administration have little to no effect on mortality in ICU patients with septic shock but did demonstrate the safety of relative fluid restriction.[29,30] Several ongoing studies including ARISE FLUIDS, EVIS, and FRESHLY will generate additional data on the potential benefits of conservative fluid strategies and early vasopressor use in septic shock.[31–33] In the meantime, based on the observational data that fluid overload is associated with mortality and accumulating RCT data that conservative fluid management is at worst safe, a reasonable modern approach to fluid management includes aiming to achieve an even to net negative fluid balance at 72 hours and keeping cumulative fluid balances low to avoid end-organ dysfunction resulting from volume overload.

De-resuscitation: the practice of fluid mobilization, evacuation, or 'de-resuscitation' has gained traction in recent years as a way to minimize adverse effects of volume overload and potentially decrease duration of illness (Figure 1). Although minimal prospective literature on this approach currently exists in the realm of sepsis, the REDUCE trial aims to explore the feasibility of a protocol for in-ICU de-resuscitation. With the ongoing RELIEVE-AKI and Probe-Fluid trials that are studying fluid management using RRT in patients with acute kidney injury (AKI) in the ICU, we may soon have more guidance into optimal strategies for managing fluid overload in critical illness.[33,38,39]

Perfusion assessment

In the assessment of perfusion in sepsis, intensivists have historically focused on normalizing macro-haemodynamic parameters. The targeted goals for resuscitation have evolved from static haemodynamic targets (e.g. heart rate, mean arterial pressure, central venous pressure) to dynamic variables such as pulse pressure variation, stroke volume variation, plethysmography variability index, and others obtained through bedside echocardiography measurements.

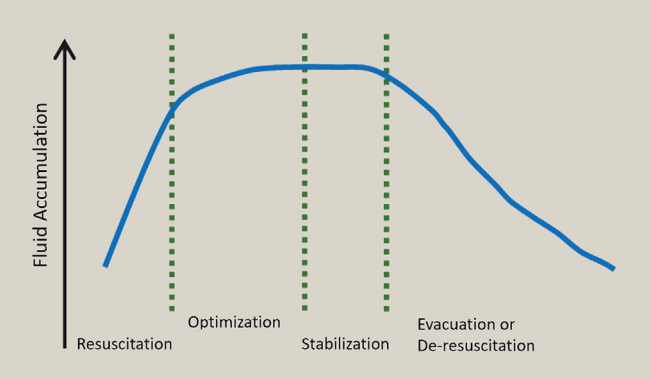

Figure 1 The four phases of fluid therapy in sepsis or other critical illness: 'ROSE'. Optimal fluid resuscitation strategies should parallel the phases of septic shock or other critical illness. The first phase (e.g. first 6 hours) is **R**esuscitation, when initial aggressive resuscitation, recommended to be 30 ml/kg ideal body weight of crystalloid in most patients,[34] should be provided. The second phase is **O**ptimization, when additional fluids are given specifically targeting fluid responsiveness (i.e. increased stroke volume or cardiac output) or other specific haemodynamic endpoints to improve organ function. The third phase is **S**tabilization, also referred to as the 'tone and time' phase, in which patients remain on vasopressors but vasopressor requirements are no longer increasing, patients are no longer fluid responsive, organ function is stable or improving, and further fluids are withheld. The fourth phase is **E**vacuation, also known as the de-resuscitation or mobilization phase, when patients with volume overload are treated with diuretics or ultrafiltration to expedite the return to euvolaemia in hopes of accelerating recovery from critical illness.[35–37] The time at which a given patient transitions between phases varies and repeated insults may substantially disrupt this sequence. Reproduced with permission from Hoste et al. *Br J Anaesth* 2014.[36]

However, persistent alterations of microcirculatory blood flow *despite* the restoration of macro-haemodynamic parameters can lead to organ failure. At least one study has shown that microcirculatory perfusion alterations predicted mortality during serious infection, whereas mean arterial pressure and cardiac output did not.[38]

This dissociation between microcirculatory and microcirculatory flow underscores the need to assess end-organ tissue perfusion in patients with septic shock and to develop tools to analyse microcirculatory blood flow. For example, persistent hyperlactatemia has been traditionally considered as a signal of tissue hypoperfusion or hypoxia. Consequently, lactate normalization is recommended as a resuscitation target in recent guidelines.[14] However, the pathogenesis of lactic acidosis is sepsis metabolically complex, and many have recently criticized the use of lactate as a haemodynamic endpoint of resuscitation, especially when used as a trigger for further IV fluid administration.[39]

Peripheral perfusion is a promising alternative target. There is particular interest in the scientific community for using the skin, an easily accessible organ, as a surrogate for deeper organ perfusion by using skin temperature gradients, capillary refill time (CRT), the extent of mottling, and the peripheral perfusion index.

In the first major RCT using peripheral perfusion as an assay for microcirculatory dysfunction (ANDROMEDA-SHOCK), a CRT-targeted resuscitation strategy did not demonstrate a statistically significant reduction in all-cause 28-day mortality when

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compared to lactate-targeted fluid resuscitation, though there was a trend ($p = 0.06$) towards benefit. This trial also demonstrated that CRT could be used to reliably follow dynamic changes in regional and microcirculatory flow parameters and hypoxia surrogates during sepsis resuscitation.[40] A much larger follow up trial (ANDROMEDA-SHOCK-2) is in progress and aims to further stratify patients in septic shock in order to more precisely guide CRT-based resuscitation efforts.[41]

Given the subjectivity of CRT, several new technologies have been developed to more objectively measure CRT, and other methods for the objective assessment of peripheral perfusion are in development, all in the hope of identifying better microcirculatory targets for resuscitation.[42] The overall efficacy of microcirculation-targeted resuscitation remains to be determined, however.

Vasopressors

Mean arterial pressure (MAP) is the primary driving factor behind systemic perfusion. When hypotension persists despite adequate IV fluid resuscitation, vasopressors should be promptly administered. At present, the SSC recommends noradrenaline (norepinephrine) as the first-line vasopressor.[43] If a second agent is necessary to achieve MAP goals, vasopressin is recommended.

Patients with septic shock are hypothesized to have a 'relative vasopressin deficiency', meaning that levels of vasopressin are lower than expected for a shock state.[44] Thus, the addition of low-dose vasopressin or analogues can be effective treatments for refractory shock. Furthermore, the addition of vasopressin has been noted to have a dose-sparing effect on norepinephrine requirements, potentially decreasing the risk of tachyarrhythmia[45,46] and other catecholamine-associated side-effects.[47] In addition, vasopressin has been proposed to have a nephroprotective effect in septic shock, but this effect was not seen when assessed as the primary outcome of the large VANISH RCT.[48,49]

Though previously recommended as an alternative to vasopressin as a second-line vasopressor for septic shock, 2021 SSC guidelines recommend adrenaline (epinephrine) as a third-line agent, particularly for patients with cardiac dysfunction.[10] Notably, given its stability at room temperature, adrenaline remains a frequently used first-line agent for septic shock in resource-limited settings. In low doses, adrenaline is an inotrope, but at higher doses it can manifest vasoconstrictive properties. Head-to-head comparisons of adrenaline to noradrenaline or to noradrenaline and dobutamine in septic shock showed no difference in mortality but increased adverse events with adrenaline versus noradrenaline alone.[46,50] Notably, adrenaline infusions, via the metabolic effects of β-2 receptor stimulation, almost invariably cause hyperlactatemia, and, though adrenaline-induced lactic acidosis has been associated with *reduced* mortality,[51] this effect nonetheless limits the usefulness of lactate clearance as an indicator of response to therapy in adrenaline-treated patients.

Previously considered the first-line vasopressor for septic shock, dopamine has fallen out of favour since the 2010 SOAP II RCT.[52] A subsequent 2015 meta-analysis found decreased all-cause mortality with norepinephrine compared to dopamine in septic shock.[53] Dopamine should be reserved for select patients (e.g. septic patients with bradycardia).[54]

There are extremely limited clinical trial data about the use of phenylephrine in septic shock, with observational data suggesting that phenylephrine in septic shock is associated with higher mortality rates when compared to noradrenaline.[55,56] As such, its use should be limited in patients with sepsis.[53]

Angiotensin II (ATII) is the most recent vasopressor to receive European Medicines Agency and US Food and Drug Administration approval following the 2017 ATHOS-3 trial. In this multicentre RCT the group treated with ATII demonstrated a significant increase in blood pressure and no significant increase in adverse events.[57] ATII appears to be particularly effective in patients with AKI, as a subgroup analysis of the ATHOS-3 demonstrated a mortality benefit in patients with AKI requiring RRT.[58] Additionally, results from a recent observational pilot study suggest that ATII may be effective when used as a first-line vasopressor for vasodilatory shock, but additional data to define which patients are most likely to derive benefit from ATII are needed.[59]

A subset of patients with septic shock will develop septic cardiomyopathy. These patients typically have little cardiac reserve at baseline and are unable to generate a compensatory cardiac output during vasodilatory shock. If cardiac output remains low despite use of vasopressors, initiation of inotropic therapy is appropriate. The 2021 SSC guidelines recommend the addition of dobutamine to noradrenaline or switching from noradrenaline to adrenaline, as data show similar improvements in cardiac output with the use of single-agent adrenaline compared to dobutamine paired with noradrenaline.[14,50]

Diagnostic techniques

Microbiological cultures

Positive blood cultures are demonstrable evidence of systemic infection. If sepsis is suspected, current guidelines recommend drawing two sets of blood cultures, both aerobic and anaerobic. However, blood culture yield is variable and is dependent upon sampling technique. Care must be taken to adequately prepare the skin with antiseptic agent and to inoculate each bottle with a minimum of 10 ml of blood. Ideally, cultures should be obtained prior to the administration of antibiotics to improve yield. Cultures of other bodily fluids should also be obtained as clinically indicated (e.g. sputum, urine, cerebrospinal fluid, etc.).[60]

Lactate

As mentioned above, the use of lactate as an endpoint of resuscitation in sepsis has been recently questioned. Undeniably, an elevated serum lactate level is a marker of disease severity in sepsis. Likewise, the normalization of lactate with resuscitation in early sepsis is predictive of a good outcome.[61] However, the aetiology of the rise in lactate is multifactorial, potentially including anaerobic metabolism resulting from inadequate oxygen delivery but also including a variety of metabolic perturbations unrelated to fluid status. Prior RCT data suggested that lactate-guided resuscitation in patients with septic shock reduced mortality, though this finding has not been consistently reproduced. Despite this controversy, the 2021 SSC guidelines continued to suggest the use of lactate clearance as a resuscitation goal (albeit a weak recommendation based on low-quality evidence) and elevated lactate levels are part of the current criteria for the diagnosis of septic shock.[4,40,62,63]

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Biomarkers

Numerous novel biomarkers (e.g. suPAR, presepsin, cell-free plasma DNA) are under study with the aim of improving diagnostic precision and prognostication and ultimately predicting treatment response. However, most have not shown the sensitivity, specificity, or cost-efficacy needed to justify their use in clinical practice.[64]

Procalcitonin (PCT) is the most studied sepsis biomarker.[65] A precursor to the hormone calcitonin, levels are routinely elevated in the setting of systemic infection. Thus far, studies show procalcitonin to be useful in decreasing the duration of antibiotic treatment, healthcare costs, the length of hospitalization, and adverse events.[66,67] That said, elevations of PCT can also be seen in uninfected patients. For example, modest elevations in PCT are common in patients with renal disease, requiring adjusted interpretation. Based upon available data, the SSC suggests using procalcitonin only to limit or discontinue antibiotic therapy. It should be emphasized that elevated or normal procalcitonin levels alone are insufficient to justify the initiation (or not) of antibiotics.[43]

Molecular techniques

Identifying and treating an offending organism in a timely manner is often a challenge. Conventional blood cultures can take up to 72 hours to provide a definitive result, while recently developed molecular techniques can detect pathogens far more quickly. Ongoing evaluations of pathogen identification techniques using multiplex polymerase chain reaction (PCR), PCR-electrospray ionized mass spectroscopy (ESI-MS), and functionalized nanoparticles coupled with magnetic resonance have demonstrated the capability of identifying organisms in under 6 hours with reasonable sensitivity and specificity. Further studies and cost analyses will determine whether these techniques are incorporated into general clinical practice, but in the near future these techniques may very well obviate the need for conventional blood cultures.[68]

Molecular phenotyping and treatment enrichment strategies

Recent research has shown that sepsis may be far more heterogeneous than once thought. In 2017, Scicluna et al. analysed a cohort of patients with sepsis and found markedly different genomic endotypes associated with a spectrum of hyperinflammatory or hypoinflammatory responses to infection.[69] They demonstrated that the subjects on either extreme had higher mortality rates than those that exhibited a more measured or balanced response, leading to the suggestion that sepsis treatments tailored to an individual's inflammatory phenotype or endotype may improve outcomes.

Subsequent research has further classified sepsis into distinct phenotypes that present with a myriad of clinical presentations, laboratory abnormalities, and patterns of organ dysfunction.[70,71] Furthermore, these genetic subgroups have been shown to be associated with different responses to pro- and anti-inflammatory modulators, leading to the potential for tailored treatment based on phenotypic or endotypic classification.[70] Currently, large trials are in process exploring tailored treatments for specific sepsis subgroups and biomarker enriched (selected) sepsis sub-populations.[72–74]

Adjunctive therapies

Steroids

Despite dozens of trials, the role of corticosteroids in sepsis remains controversial. The 2021 SSC guidelines recommended 200 mg per day of IV hydrocortisone either given 50 mg IV every 6 hours or as a continuous infusion for patients who have persistent circulatory failure despite adequate fluid resuscitation and vasopressor therapy defined as a dose of noradrenaline $\geq$0.25 micrograms/kg/minute at least 4 hours after initiation. This recommendation is largely based on two recent major corticosteroid trials with somewhat discordant results. The ADRENAL trial randomized septic shock patients to receive hydrocortisone versus placebo, and while no difference in mortality was noted, there was a significant improvement in reversal of shock, ICU length of stay, ventilator-free days, and need for blood transfusions.[75] On the other hand, another multi-centre RCT administering hydrocortisone plus fludrocortisone versus placebo to patients in septic shock did find a reduction in all-cause mortality in the treatment group, along with shorter durations of shock, ICU length of stay, and organ support.[76] Much like the evidence, the critical care community remains divided on the use of steroids in septic shock.

Vitamin C ($\pm$thiamine)

The use of vitamin C in patients with sepsis and septic shock is no longer recommended in the latest SSC guidelines.[10] Since a heavily publicized observational study in 2017 that claimed a reduction in mortality, *multiple* subsequent RCTs have failed to show benefit, and, in some cases, have demonstrated harm.[77–79]

Blood purification techniques

Endotoxin is circulating in 50% of patients in septic shock and is associated with poor outcomes.[80] The EUPHRATES trial attempted to neutralize endotoxin via haemoperfusion with a polymyxin fibre device.[81] EUPHRATES was the largest RCT to study this technology but was terminated early due to a failure to achieve the primary mortality endpoint. However, while it did fail to show a mortality benefit in the overall trial population, a post-hoc analysis found that polymyxin B haemoperfusion decreased mortality in a subset of patients with moderate endotoxin activity (EA) as opposed to extreme EA.[82] Based on these findings, the TIGRIS trial is currently enrolling patients to evaluate haemoperfusion in patients with moderate-EA septic shock.[83] Other techniques, such as extracorporeal plasma filtration to remove pro- and anti-inflammatory mediators from the bloodstream are under evaluation.[84,85] While the concept remains appealing, at this time data are lacking to support the routine adoption of any blood purification technologies for sepsis.

Glycaemic control

Glycaemic control in sepsis is a much-debated topic. On one hand, hyperglycaemia can exert an immunosuppressive effect, diminishing the body's ability to mount a competent immune response. On the other, the anti-inflammatory effects of insulin may inhibit cellular autophagy and negatively impact a patient's capacity to clear infection.[86]

Evidence shows that severe hyperglycaemia in patients with sepsis is associated with increased 30-day mortality.[87] On the

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other hand, the NICE-SUGAR trial, a large multicentre RCT, compared intensive insulin control (targeting blood glucose 81−108 mg/dl) to conventional insulin control (<180 mg/dl) and found increased rates of hypoglycaemia and mortality with intensive insulin therapy.[88] As both hyperglycaemia and hypoglycaemia are associated with adverse outcomes, current recommendations are to start insulin after blood glucose levels exceed 180 mg/dl (10 mmol/litre) with the goal of maintaining levels <180 mg/dl. There is no specific lower threshold target, but avoidance of hypoglycaemia or wide swings in glucose levels is advised.

Anticoagulants (including thrombomodulin)

The use of thrombomodulin for treatment of sepsis-induced disseminated intravascular coagulation (DIC) has been well established in Japan for several years,[89] and the SCARLET trial sought to determine if the benefit would extend to a more heterogeneous population. Unfortunately, this large international RCT failed to demonstrate any mortality benefit in patients with sepsis-associated coagulopathy.[90] Other anticoagulants, such as antithrombin and (therapeutic dose) heparin have also been studied,[91,92] yet neither are recommended as a therapeutic modality. However, prophylactic anticoagulant use remains recommended in the SSC guidelines.[43]

Intravenous immunoglobulin

Acquired immunosuppression leading to low endogenous immunoglobulin levels may impact mortality in patients with sepsis.[93] Thought to mitigate the inflammatory response and augment immune mechanisms, IV immunoglobulin (IVIG) has the potential to modulate both pro- and anti-inflammatory processes. Thus far, however, IVIG (especially isolated immunoglobulin (Ig) G IVIG) has not been shown to improve mortality in patients with sepsis.[94] While the infusion of a polyclonal IVIG containing IgG, IgA and IgM showed more promising results, including a modest reduction in mortality, reliable data regarding timing and dosing of IVIG are still lacking to justify its routine use.[95,96] As such, IVIG is not currently recommended as a therapeutic agent for the treatment of sepsis.

Conclusions

Sepsis and septic shock are leading contributors to worldwide morbidity and mortality. The current definitions of sepsis and septic shock are based upon an expanded understanding of sepsis as a dysregulated immune response as opposed to solely an inflammatory process. Early recognition and prompt management, such as the implementation of the 1-Hour Bundle for septic shock, are essential to improving patient outcomes. The core elements of any treatment algorithm remain the same: antibiotics, source control, intravenous fluid resuscitation, and vasopressors, tempered with the recognition that sepsis is not a static process and that frequent reassessment and revision of the treatment plan are essential. A number of potential targeted adjunctive therapies and novel diagnostic techniques are on the horizon, though none yet have a role in routine clinical practice. ◆

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